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Recent findings on the therapeutic effects of pilocarpine on dry mouth

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Pilocarpine, used as a treatment for dry mouth, is a partial agonist of muscarinic acetylcholine receptors (mAChRs), and induces salivation through a rise in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) by activating mAChRs in salivary acinar cells. In rodents, a 0.1~10 mg (mg/kg, intraperitoneal administration) dose of pilocarpine induces salivary secretion. Such a dose is similar to a 3~100 μM (0.7~35 μg/mL) concentration which increases the $[Ca^{2+}]_i$ in isolated salivary gland cells (Fig 1A, Nezu et al., 2015).

Clinically, pilocarpine (Salagen® tablets) is prescribed orally in a dosage of 5 mg/tablet. According to the instructions provided with Salagen® tablets, this dose of pilocarpine does not cause salivation after oral administration, but improves salivation after continuous administration of pilocarpine for more than 12 weeks. The maximum blood concentration (C_{max}) of a single oral dose of pilocarpine is around 30 ng/mL. This concentration is estimated to be approximately 0.1 μM, less than one−thirtieth of the concentration that increases $[Ca^{2+}]_i$ in *in vitro* experiments. This suggests that mechanisms other than the mAChR−mediated Ca^{2+} responses may be involved in the improvement of salivation by Salagen® tablets (Fig. 1A). Recently, Minagi−Ono et al. (2018) reported what may provide a possible answer to the mechanism for improving salivation by Salagen® tablets.

At Osaka University Dental Hospital, pilocarpine is used for patients with Sjögren's syndrome (SS). The hospital prescribes pilocarpine at about half of the usual dose to reduce side effects such as nausea, and examined salivary secretions by the Saxon test and the visual analog scale after the treatment for more than 12 weeks. The results showed significant improvements in these evaluations, indicating that continuous administration of pilocarpine improves the salivary function in SS patients, even at low doses (Minagi−Ono et al., 2018).

Next, Minagi−Ono et al. analyzed salivary secretion, cell morphology, protein, and gene expression after a continuous oral administration of the low−dose of pilocarpine in wild type and SS model mice. Two−weeks of pilocarpine (1 mg/10 mL/kg, orally, Twice daily) administration significantly increased salivary secretion in these mice. This study also showed a significant increase in the protein and gene expression of M_3 mAChR in the salivary glands of the pilocarpine−treated mice (Fig. 1B), suggesting that the increase in the expression level of M_3 mAChR may contribute to the improvement of salivary secretion (Minagi−Ono et al., 2018).

Pilocarpine has been thought to improve salivation via the Ca^{2+}−dependent fluid secretion in the treatment of dry mouth by Salagen® Tablets. This study provides new insight into the mechanism by which pilocarpine improves dry mouth : the up−regulation of the expression of M_3 mAChR in salivary gland cells (Fig. 1B). The mechanism for the increase in the expression of M_3 mAChR by pilocarpine remains unclear. Elucidation of this mechanism may lead to the development of a new treatment for dry mouth.

References

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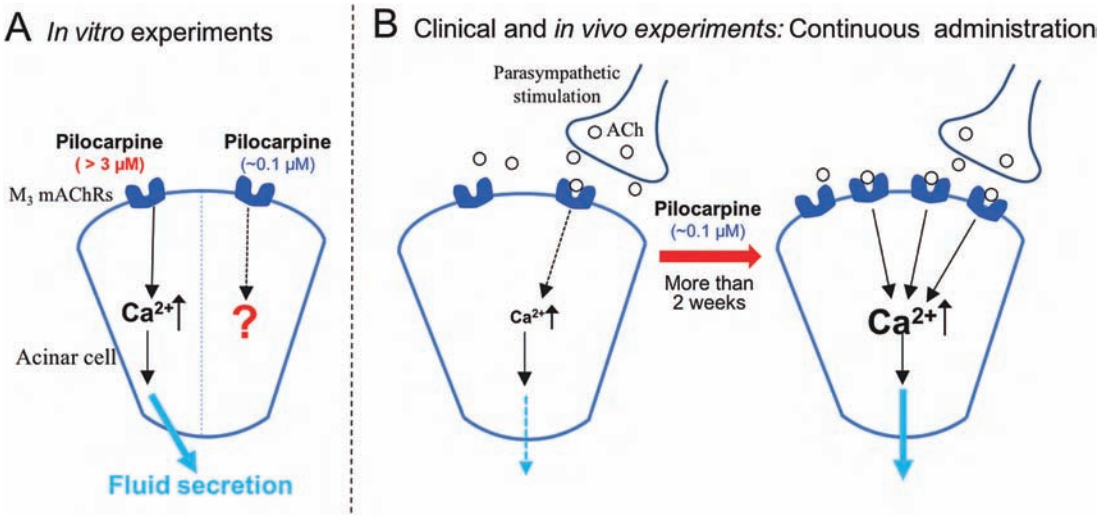

Figure 1 : Mechanism of the therapeutic effect of pilocarpine with dry mouth.
A) Mechanisms of pilocarpine−induced salivary fluid secretion through the activation of mAChR in *in vitro* experiments. B) Mechanisms of continuous administration of pilocarpine in clinical and *in vivo* experiments. ACh : acetylcholine.